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EXAMINER	
WOLLENBERGER, LOUIS V	

ART UNIT	PAPER NUMBER
1635	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/824,939	CRABTREE ET AL.	
	Examiner	Art Unit	
	Louis V. Wollenberger	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 January 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7 and 20* is/are pending in the application.

4a) Of the above claim(s) *2,3,5-7 and 20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 4* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *15 April 2004* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *8/2/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicants' timely election, with traverse, of Group III, Claim 4, in the reply filed on Janury 10, 2006, is acknowledged.

The traversal is on the ground(s) that it would not be a serious burden on the Examiner to search all claims in Groups I-VI together in the same application. Applicants state that the claims in Groups I-VI share the same class and subclass and are directed to methods for promoting axonal growth comprising treating a neuron with an NF-AT agonist. Applicants argue that a species restriction is more appropriate in that the groups differ in the way that the NF-AT agonist is characterized.

Applicants' arguments have been fully considered but are not found persuasive.

While it may be true that the groups are all classified in the same class/subclass; 514/44 comprises a multitude of different inventions, which would require further sorting by keyword and keyword combinations to identify subject matter pertinent to the instant claims. As explained in the Requirement, Groups I–VI are unrelated, and, therefore, independent and distinct, because they are drawn to methods that require the use of structurally and functionally distinct molecules, that have different modes of operation in the cell, i.e., that act through different mechanisms. For instance, calcineurin and agents that activate or upregulate the expression of calcineurin may be expected to have different structures and act by a different mechanisms as compared to agents that bind NF-AT or inhibit GSK3 expression, such as antisense, ribozymes, or DNA enzymes.

Similarly, agents that directly interact with calcineurin, the protein, (claim 2), may be structurally and functionally distinct from agents that activate or upregulate the expression of calcineurin.

Thus, a serious burden exists since groups I–VI comprise claims to different methods requiring different molecules and agents, requiring searches that are divergent and not necessarily co-extensive. Further, a search and examination of the claims involves considerations of novelty, obviousness, written description, and enablement for each claim. In view of these requirements, it is the Examiner's position that searching and examining all of the claims in groups I–VI in the same application presents a serious burden on the Examiner for the reasons given above and in the previous Restriction Requirement.

The requirement is still deemed proper and is therefore made FINAL.

Status of the application

With the amendment of 1/1/06, Claims 1–7 and 20 are pending.

Claims 2, 3, 5-7, and 20 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Claims 1 and 4 are examined herein.

Drawings

MPEP §608.02, Section VIII, states in part that:

Limited use of color drawings in utility patent applications is provided for in **37 CFR 1.84(a)**(2) and (b)(2). Unless a petition is filed and granted, color drawings or color photographs will not be accepted in a utility or design patent application. The examiner must object to the color drawings or color photographs as being improper and require applicant either to cancel the drawings or to provide substitute black and white drawings.

> Under **37 CFR 1.84(a)**(2) and (b)(2), the applicant must file a petition with fee requesting acceptance of the color drawings or color photographs. Three sets of color drawings or color photographs must also be submitted (**37 CFR1.84(a)(2)(ii)**). **The petition is decided by a Supervisory Patent Examiner. See **MPEP § 1002.02(d)**.

It is noted that Applicants have submitted color drawings and/or photographs as part of the instant application. See Figs. 1-12, for example. Color photographs and color drawings are not accepted unless a petition filed under 37 CFR 1.84(a)(2) is granted. Any such petition must be accompanied by the appropriate fee set forth in 37 CFR 1.17(h), three sets of color drawings or color photographs, as appropriate, and, unless already present, an amendment to include the following language as the first paragraph of the brief description of the drawings section of the specification:

> The patent or application file contains at least one drawing executed in color. Copies of this patent or patent application publication with color drawing(s) will be provided by the Office upon request and payment of the necessary fee.

Color photographs will be accepted if the conditions for accepting color drawings and black and white photographs have been satisfied. See 37 CFR 1.84(b)(2).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1 and 4 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant

art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Factors to be considered in determining whether there is sufficient evidence of possession include the level of skill and knowledge in the art, complete or partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention. Disclosure of any combination of such identifying characteristics that distinguish the claimed invention from other materials and would lead one of skill in the art to the conclusion that the applicant was in possession of the claimed species is sufficient.

The claims are drawn to a method for promoting axonal growth comprising treating a neuron with an NF-AT agonist, and to a method thereof wherein the NF-AT agonist is calcineurin or an agent that "activates or upregulates the expression of calcineurin." Accordingly, claim 4 is interpreted to encompass calcineurin—the protein—and agents that directly or indirectly activate or upregulate the expression of calcineurin, as by transcriptional activation or other suitable mechanisms.

Thus, the claims are extremely broad. For example, in their broadest embodiments the claims include methods for promoting axonal growth using any NF-AT agonist. Further, the claims encompass methods for promoting axonal growth using any agent that activates or upregulates the expression of calcineurin. The specification explicitly states that the term "NF-AT agonist" refers to any refers to any molecule which activates or potentiates NF-AT dependent gene transcription (page 13). For example, NF-AT agonists include, but are not limited to,

> "molecules that: (1) interact directly with NF-AT and modulate its nuclear translocation and activity; (2) interact directly with calcineurin and increase the dephosphorylation and/or activation of NF-AT; (3) interact directly with calmodulin and increases the activity of calcineurin and the dephosphorylation and/or activation of NF-AT; (4) stimulate an increase in intracellular calcium concentration which induces the activation of calcineurin and the dephosphorylation of NF-AT; (5) bind to a cell surface receptor and induce an increase in intracellular calcium concentration which induces the activation of calcineurin and the dephosphorylation of NF-AT; (6) interact with and inhibits GSK3 or other NF-AT kinases which functions to increase the nuclear duration and activity of NF-AT; (7) modify the DNA interaction of NF-AT in order to increase NF-AT dependent transcription; or (8) modify the interaction of NF-AT with a nuclear partner that results in an increase in transcription. An NF-AT agonist may also be a molecule which increases or enhances the expression of NF-AT." (pages 13-14).

The specification goes on to state that NF-AT agonists may be small organic molecules or other biological molecules such as nucleic acids or proteins (page 16). Further, according to the specification, compounds that antagonize, inhibit, or suppress the activity of GSK3 are NF-AT agonists (page 23)

Thus, NF-AT agonists include a wide variety of structurally and functionally diverse small molecules, organic and inorganic substances, peptides, recombinant proteins, polynucleotides—including antisense oligos, ribozymes, and siRNAs—lipids, and polysaccharides, to name but a few, which are capable of inhibiting NF-AT activity and/or expression either directly or indirectly through any number of different biochemical and molecular biological mechanisms.

Additionally, albeit more specifically, the method encompasses the use of any agent that activates or upregulates the expression of calcineurin.

Adequate written description does not exist in the instant application for all these methods. That is, the specification does not adequately allow persons of ordinary skill in the art to recognize that applicant(s) were in possession of the entire genus of NF-AT agonists and activating agents required to practice the method as now claimed. The NF-AT agonists and

calcineurin expression activators or upregulators required for the methods are recited in terms of their function only; there is no art-recognized correlation between the structure of these substances and their function, and the specification does not provide the support needed to enable one skilled in the art to predict with a reasonable degree of confidence the structure of the requires agents and agonists from a recitation of function only. In fact, while applicants have described several specific substances for use in the claimed method, applicants have not provided any guidance or structurally-based starting point—i.e, a core structure or sequence essential to the activity of the agonist—which would enable the skilled artisan to envision all other organic and inorganic, small and large molecule NF-AT agonists and calcineurin expression activators.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed (pg. 1117). Because the level of skill and knowledge in the art increases over time, it is essential to determine possession as of the effective filing date.

A disclosure in a parent application that merely renders the later-claimed invention obvious is not sufficient to meet the written description requirement; the disclosure must describe the claimed invention with all its limitations." (Tronzo v. Biomet Inc., 156 F.3d 1154, 1158, 47 USPQ2d 1829, 1832 [Fed. Cir. 1998]). The specification need not, however, describe the claimed invention using the same words as the claims (Purdue Pharma L.P. v. Faulding, Inc., 230 F.3d 1320, 1323, 56 USPQ2d 1481, 1483 [Fed. Cir. 2000]).

Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The compound itself is required.

See *Fiers v. Revel,* 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.,* 18 USPQ2d 1016.

In the instant case, the specification does not clearly allow persons of ordinary skill in the art to recognize that Applicants invented what is now claimed. The application does not enable the skilled artisan to clearly envision the detailed chemical structure of the encompassed genus of NF-AT agonists and agents that activate or upregulate the expression of calcineurin, and, thereby, promote axonal growth of any neuron in vitro or in vivo. In fact, a review of the instant application and the prior art fails to find written description of even a single agent capable of specifically activating or upregulating the expression of calcineurin in neurons.

An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997).

While the specification and prior art (Ming et al. 2002, for example, cited in IDS) adequately describes certain specific NF-AT agonists, such as netrin-1, by fully setting forth their structures and functions, and by describing the materials and methods needed to make and use such agents, adequate written description does not exist for the virtually unlimited number of other agonists in the claimed genus. Thus, applicants have not shown possession of the claimed methods using all possible NF-AT agonists to promote axonal growth in neurons.

Furthermore, Applicants have not shown possession of the claimed methods using all possible agents that activate or upregulate calcineurin expression. In fact, it is unclear what if any agent may be used to specifically activate or upregulate calcineurin expression. While the protein

itself is defined in the prior art, agents that specifically activate the transcription and/or translation of the protein have not been defined.

Accordingly, only methods comprising the use of structurally defined molecules, compounds, and compositions capable of agonizing NF-AT, such as calcineurin and netrin-1, and/or that activate expression of calcineurin, meet the written description requirement.

Applicant is reminded that the written description requirement is separate and distinct from the enablement requirement. *In re Barker*, 559 F.2d 588, 194 USPQ 470 (CCPA 1977), cert. denied, 434 U.S. 1064 (1978); *Vas-Cath, Inc.* v. *Mahurkar*, 935 F.2d 1555, 1562, 19 USPQ2d 1111, 1115 (Fed. Cir. 1991).

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Claims 1 and 4 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

> methods of promoting axonal growth of rat dorsal spinal cord neurons in cell culture *in vitro* by treating the neuron with netrin-1,

does not reasonably provide enablement for:

> methods of promoting axonal growth of a neuron *in vivo* by treating the neuron with any NF-AT agonist, calcineurin protein, or any agent that activates or upregulates the expression of calcineurin.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Factors to be considered in a determination of lack of enablement include, but are not limited to:

(A) The breadth of the claims;

(B) The nature of the invention;

(C) The state of the prior art;

(D) The level of one of ordinary skill;

(E) The level of predictability in the art;

(F) The amount of direction provided by the inventor;

(G) The existence of working examples; and

(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)

The claims are described above.

The invention is considered to be in a class of invention that the CAFC has characterized as "the unpredictable arts such as chemistry and biology" (Mycogen Plant Sci., Inc. v Monsanto Co., 243 F.3d 1316, 1330 [Fed. Cir. 2001]).

As explained above, the claims are extremely broad. For instance, in their broadest embodiments the claims encompass methods for promoting axonal growth of any neuron in or from the peripheral or central nervous system, including the brain, either *in vitro* or *in vivo*, using

any NF-AT agonist, calcineurin protein, or agent that activates or upregulates calcineurin expression.

Thus, the claimed methods encompass methods of gene therapy, and include methods of promoting axonal nerve growth in mammals, including humans, using, for example, nucleic acids such as antisense oligonucleotides, ribozymes, and/or siRNAs directed to, for example, GSK3 (see pages 13 and 18-22 of the specification, for example) The claimed methods also encompass the use of antibodies, recombinant proteins, peptides, and small molecules.

To be clear, the instant rejection has at least three bases. One is the unpredictability in the art as it relates to the delivery of NF-AT agonists—peptides, proteins, antibodies, and nucleic acids—to neurons *in vivo,* so as to elicit the desired effect in the target cell. A second basis is the complexity and wide range of cellular and physiological functions mediated by calcineurin, an NF-AT agonist within the scope of claim 1 and specifically recited in claim 4. In this respect, treating a neuron in vivo with an NF-AT agonist such as calcineurin or, even, netrin-1 is expected to produce a variety of responses in the cell and the subject as a whole. A third basis is the lack of adequate representation either in the specification or the prior art teaching one of skill in the art how to promote axonal growth in neurons in vivo using any and all NF-AT agonists.

With regard to the primary basis of the rejection, the post-filing art indicates that the art of gene therapy in general, and, in particular, the *in vivo* delivery of proteins and nucleic acids such as antisense oligonucleotides and siRNAs, into targeted cells, tissues, and organs was highly unpredictable at the time the instant application was effectively filed. Unpredictability in the art as it relates to nucleic acids, for example, stems mainly from the inability to routinely

deliver an effective concentration of a specific nucleic acid into a target cell, such that a target gene is inhibited to a degree necessary to produce a therapeutic effect.

For instance, if one were to choose an anti-GSK3 antisense oligonucleotide or siRNA as the NF-AT agonist, as taught by the instant application, one would be faced with several challenges. The primary factors appear to be delivery, uptake, stability, and biological effect in host organisms, which cannot be predicted *a priori* based on cell culture experiments.

For instance, Crooke (2001) in Antisense Drug Technology, Chapt. 1, Basic Principles of Antisense Technology, pp. 1-28 (Springer-Verlag) states on page 8 that

> "...conclusions about in vitro uptake must be very carefully made and generalizations are virtually impossible." "...extrapolations from in vitro uptake studies to predictions about in vivo pharmokinetic behavior are entirely inappropriate and, in fact, there are now several lines of evidence in animals and humans that, even after careful consideration of in vitro uptake data, one cannot predict in vivo pharmokinetics of the compounds."

Opalinska et al. (2002) *Nature Reviews* 1:503-514 teach that

> "[I]t is widely appreciated that the ability of nucleic-acid molecules to modify gene expression *in vivo* is quite variable, and therefore wanting in terms of reliability. Several issues have been implicated as a root cause of this problem, including molecule delivery to targeted cells and specific compartments within cells and identification of sequence that is accessible to hybridization in the genomic DNA or RNA" and in column 2 of the same page, "Another problem in this field is the limited ability to deliver nucleic acids into cells and have them reach their target. Without this ability, it is clear that even an appropriately targeted sequence is not likely to be efficient. As a general rule, oligonucleotides are taken up primarily through a combination of adsorptive and fluid-phase endocytosis. After internalization, confocal and electron microscopy studies have indicated that the bulk of the oligonucleotides enter the endosome-lysosome compartment, in which most of the material becomes either trapped or degraded." (page 511)

Lu et al. (2005) in *RNA Interference Technology* (Cambridge, Appasani, ed.) state that

> "Unlike *in vitro* transfection of siRNA into cells, *in vivo* delivery of siRNA into targeted tissue in animal models is much more complicated, involving physical, chemical and biological approaches, and in some cases their combination." Therapeutic applications, however, clearly depend upon optimized local and systemic delivery of siRNA *in vivo*. "....limited reports of *in vivo* studies have indicated a lack of effective delivery methods for siRNA agents." "...the two most critical hurdles are maintaining its [siRNA] stability *in vivo* and delivery to disease tissues and cells." (page 314) Lu et al. admit that while hydrodynamic delivery of siRNA duplexes into mouse liver has proven to be quite efficient, this technique is not clinically feasible in human studies." (page 303)

If one were to choose calcineurin as the NF-AT agonist, as claimed in claim 4, one would be faced with the complexities of the effects elicited by calcineurin.

The prior art teaches, for example, that calcineurin plays a central role in immune system function, through lymphokine, cell surface receptor, and apoptosis regulation (Crawford, US Patent Application 2003/0045679 A1, page 6). Contrary to the instantly claimed method, Crawford states that inhibition of calcineurin in the brain promotes neurite outgrowth (paragraph 65). Calcineurin is also said to mediate T-cell activation and enhance pathogen virulence (page 6).

Asai et al. (1999) *J. Biol. Chem.* 274:34450-34458 teach that high level constitutive activity of calcineurin renders neurons susceptible to apoptosis, which is directly contrary to the intended effect of the currently claimed method. It is noted that the instant application does not teach one how to deliver an effective amount of calcineurin to a target neuron to promote axonal growth but avoid apoptosis.

Molkentin et al. (1998) *Cell* 93:215-228 teach that calcineurin induces cardiac hypertrophy, which, in mice, may progress to congestive heart failure and sudden death (page 216).

Taigen et al. (2000) *PNAS* 97:1196-1201 even suggest inhibiting not activating calcineurin to prevent cardiomyocyte hypertrophy.

Alternatively, if one were to choose a netrin as the NF-AT agonist, as taught on page 16 of the specification, one would need to know how to administer netrin so as to activate axonal growth in the desired target neurons. This does not appear to be trivial.

Serafini et al. (1994) *Cell* 78:409-424, for example, teach that netrins represent a family of secreted proteins that are relatives of lamins (page 415). It is taught that netrins have axon outgrowth activity in some but not all neurons (page 419). The reasons underlying the variability are not made entirely clear.

Thus, the prior art indicates that calcineurin may elicit many different biological responses ranging from cell activation to cell death. Similarly, netrins may have different relative effects depending on the cell type.

The instant application does not teach by way of example or technical description how to administer calcineurin, netrins, or any other NF-AT agonist to neuronal cells *in vivo* in order to specifically promote axonal growth in a particular neuron or set of neurons, while avoiding potential deleterious effects such as apoptosis and cardiac hypertrophy, which may be directly contrary to the intended effect of the claimed method.

Given the far ranging and sometimes opposing actions of calcineurin in cells, and in view of the express teachings of the post-filing art suggesting that *in vivo* delivery of genes, antisense nucleic acids, and siRNA molecules is unpredictable, it is essential that the instant application provide enabling disclosure showing how to use the invention to target the appropriate cells in any and all animals. A review of the instant application fails to find adequate representations or guidance exemplifying the *in vivo* applications currently encompassed by the instant claims. Although, applicants discuss possible methods of delivery and methods of administration of nucleic acids, these teachings are general in nature, and do not teach the ordinary artisan how to effectively deliver siRNA and antisense DNA, or combinations thereof to any target cell *in vivo*

so as to effectively reduce GSK3 gene expression, for example, and thereby promote axonal growth.

Thus, the amount of disclosure is insufficient given the level of unpredictability in the art. For example, the instant application does not appear to teach one of skill in the art how to effectively target neurons in the CNS and peripheral nerve systems, including neurons innervating skeletal muscle, so as to promote axonal growth.

The same level of unpredictability would be expected for methods of recombinant protein delivery using plasmid DNA and viral expression vectors, and even for methods comprising the administration of a protein such as calcineurin, whose far ranging properties may elicit a host of responses in many different cell types, and even opposing responses in the same cell type, and which may or may not be capable of traversing the blood brain barrier or other tissue-specific membranes to reach the intended target cell.

Given the unpredictability in the art of gene therapy and antisense and siRNA therapy *in vivo*, the skilled artisan would require specific guidance from the instant application to practice the claimed methods to promote axonal growth *in vivo* in any host, including humans, using any small or large molecule, including any protein and any nucleic acid such as any antisense, siRNA, or ribozyme to directly or indirectly agonize NF-AT. Specific guidance would be required to teach one of skill in the art how to deliver the agents and/or nucleic acids into the target neuronal cell in an amount sufficient to produce axonal growth while avoiding undesired effects, which may be directly contrary to axonal growth.

A review of the instant application finds one example, example 12, page 42, directed to the instantly claimed method. However, the example is primarily directed to the use of a single NF-AT agonist, netrin-1, in cultured cells *in vitro.* Other examples in the specification are directed to the inhibition, not the activation of calcineurin. While the example adequately demonstrates the use of netrin-1 to promote axonal growth in cultured spinal cord explants in these specific circumstances, they do not teach the administration and treatment of neurons via alternate routes of delivery using all possible NF-AT agonists in all organisms, including humans.

It is clear that the instant specification does not teach one of skill in the art how to make and use all possible NF-AT agonists to promote axonal growth in any neuron *in vivo* in any organism.

As stated above, cell culture examples are generally not predictive of *in vivo* inhibition and the methods of delivery to a cultured cell would not be applicable to delivery of oligonucleotides or other molecules to any tissue and/or cell in any organism.

Due to differences in the biochemical conditions of a cell *in vitro* versus *in vivo* the uptake and biological activity observed *in vitro* would not predictably translate to *in vivo* results.

Given these teachings, the skilled artisan would not know *a priori* whether introduction of any NF-AT agonist *in vivo* by the broadly disclosed methodologies of the instant invention, would result in the agonist reaching the proper cell in a sufficient concentration and remaining for a sufficient time to provide successful stimulation of NF-AT. In fact, the state of the art is such that the successful delivery of an oligonucleotide or gene sequence *in vivo* or *in vitro*, such

that the polynucleotide or oligonucleotide provides the requisite biological effect to the target cells/tissues/organs, must be determined empirically.

With regard to the gene therapy methods embraced by the instant claims, the specification does not provide the guidance required to overcome the art-recognized unpredictability of using nucleic acids in therapeutic applications in any organism. The teachings of the prior art does not provide that guidance, such that the skilled artisan would be able to use nucleic acid-based NF-AT agonists in the manner disclosed to produce the intended effects of promoting axonal growth.

Thus, considering the breadth of the claims, the state of the art at the time of filing, the level of unpredictability in the art, and the limited guidance and working examples provided by the instant application, the Examiner submits that the skilled artisan would be required to conduct undue, trial and error experimentation to use the claimed invention commensurate with the claims scope.

Accordingly, the instant claims are rejected for failing to comply with the enablement requirement.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this

subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1 and 4 are rejected under 35 U.S.C. 102(b) as being anticipated by Graef et al. (1999) *Nature* 401:703-708 (cited in IDS), as evidenced by Chang et al. (1995) *Nature* 376:686-690.

Graef et al. show a method for activating endogenous NF-AT proteins in cultured hippocampal neurons comprising transfecting the neurons with constitutively active calcineurin (Fig. 1c, and see page 703). Graef et al. also show a method for activating endogenous NF-AT proteins in cultured hippocampal neurons comprising treating the neurons with ionomycin, an NF-AT agonist according to page 23 of the specification (Fig. 1d, and see page 703). It is taught that both methods activate NF-AT-dependent transcription as indicated by a GFP reporter construct.

The methods taught by Graef et al. meet all of the material limitations of the instant claims and are therefore, considered to be suitable for and inherently capable of producing the desired effect of promoting axonal growth, as evidenced by Chang et al., who teach that calcineurin activates, or at the least, regulates neuritogenesis and neurite extension, possibly by activating the transcription factor NF-AT (page 686 and 687).

Accordingly, the instant claims are anticipated.

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Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by Serafini et al. (1994) *Cell* 78:409-424.

Serafini et al. show a method for treating rat dorsal spinal cord neurons with netrin-1, an NF-AT agonist, as defined by the specification at page 16 (Fig. 8, page 416). It is taught that netrin-1 not only influences nerve growth-cone extension, but also influences the direction of growth cone extension (fig. 1, for example). Materials and methods for the procedure are described in detail (pages 419-423).

Accordingly, claim 1 is anticipated.

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Claim 1 is rejected under 35 U.S.C. 102(e) as being anticipated by Butler et al. (US 2003/0211608)

Butler et al. teach methods for inhibiting the expression of glycogen synthase kinase 3 (GSK3) using antisense oligonucleotides directed to specific isoforms of GSK3. Anti-GSK3 antisense oligos are defined by the instant application as NF-AT agonists (page 19). Butler et al. specifically teach the administration of the antisense oligos to animals to treat a neurological disorder. Thus, Butler et al. teach the use GSK3 antisense oligos to treat neurons in vivo. See claim 19, for example.

Accordingly, claim 1 is anticipated.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Louis V. Wollenberger whose telephone number is 571-272-8144. The examiner can normally be reached on Mon–Fri, 8:00 am–4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's acting supervisor, Andrew Wang can be reached on 571-272-0811. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Art Unit 1635
April 18, 2006

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1635